Figure S1. The breeding scheme for the double conditional knockout mice. The generation of parental *Pten*$^{f/f}$*Grp78*$^{f/f}$ was described previously.[15] *Pten*$^{+/+}$*Grp78*$^{+/+}$*Mx1-Cre* was commercially purchased from the Jackson Laboratory. The genotypes indicated with the gray shade were used in this study. The genetic background of the parental mouse strain is indicated below within the square brackets. The numbers below the genotypes indicate the expected probability of the indicated genotype among the offspring.

Figure S2. PTEN and GRP78 were knockdown in the peripheral blood and bone marrow of mutant mice. (A) Representative PCR genotyping results from *cPten*$^{f/f}$, *cPten*$^{f/f}$*Grp78*$^{f/+}$, *Pten*$^{f/f}$*Grp78*$^{f/f}$ and *Pten*$^{f/f}$*Grp78*$^{f/+}$ peripheral blood cells 6 days post completion of pIpC treatment. (B) Representative PCR genotyping results from WT (*78*$^{f/+}$) and *Grp78* heterozygous mice (*c78*$^{f/+}$) bone marrow 6 days post completion of pIpC treatment. (C) Western blot results for detection of GRP78 protein level in the bone marrow performed in duplicates.

Figure S3. Knockdown of GRP78 suppresses ER stress induced AKT activation. (A) Western blot results of lysates from NB4 cells transfected with siRNA against *Grp78* (siGrp78) or control siRNA (sictrl), followed by 300 nM Tg treatment for the indicated time (h). (B) Quantitation of the ratio of p-AKT to total AKT in (A). The ratio at the 0 hour

time point in cells transfected with sictrl was set as 1. All data are presented as mean ± s.e (*P<0.05, *** P<0.001, Student's t-test).

Figure S4. Knockdown of GRP94 does not suppress AKT activation by serum stimulation. Western blot results of cell lysates from HL60 cells transfected with siRNA against *Grp94* (siGrp94) and control siRNA (sictrl), followed by 16 hours serum starvation, and then stimulated with 10% serum for the indicated time (h).

Figure S5. Knockdown of GRP78 sensitizes human leukemia cells to AraC. Viability of NB4 cells transfected with siRNA against *Grp78* (siGrp78) or control siRNA (sictrl) followed by the indicated AraC concentration for 24 hours was measured by trypan blue exclusion assay. 10,000 cells/well were plated into a 96-well plate and treated with either PBS 5 μM or 10 μM AraC for 24 hours. Trypan blue solution (0.4%, Sigma) was added into the medium at 1:1 dilution and incubated for 5 minutes. The numbers of trypan blue positive cells and total cells were counted using a hemocytometer. The data are presented as mean ± s.e (**P<0.01, Student's t-test).

Figure S1

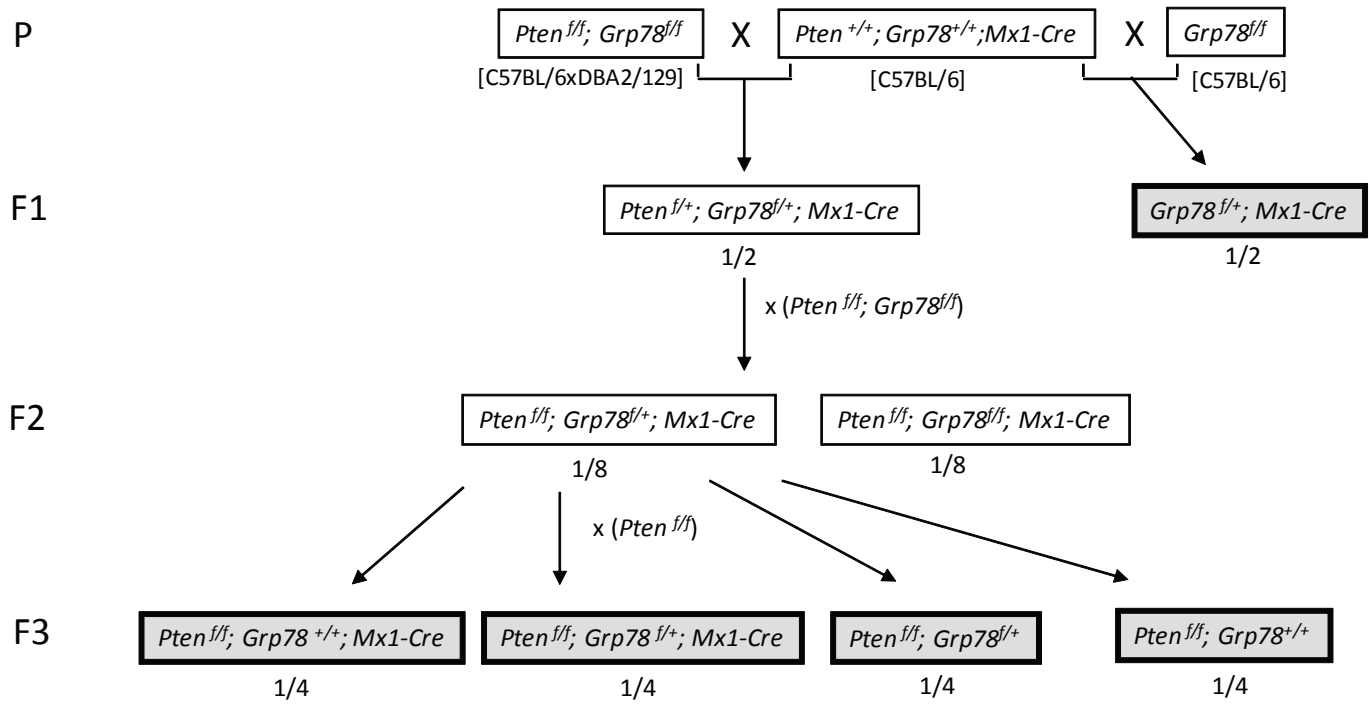

P
Pten f/f; Grp78 f/f
[C57BL/6xDBA2/129]
X
Pten +/+; Grp78 +/+;Mx1-Cre
[C57BL/6]
X
Grp78 f/f
[C57BL/6]
F1
Pten f/+; Grp78 f/+; Mx1-Cre
1/2
Grp78 f/+; Mx1-Cre
1/2
x (Pten f/f; Grp78 f/f)
F2
Pten f/f; Grp78 f/+; Mx1-Cre
1/8
Pten f/f; Grp78 f/f; Mx1-Cre
1/8
x (Pten f/f)
F3
Pten f/f; Grp78 +/+; Mx1-Cre
1/4
Pten f/f; Grp78 f/+; Mx1-Cre
1/4
Pten f/f; Grp78 f/+
1/4
Pten f/f; Grp78 +/+
1/4

Figure S2

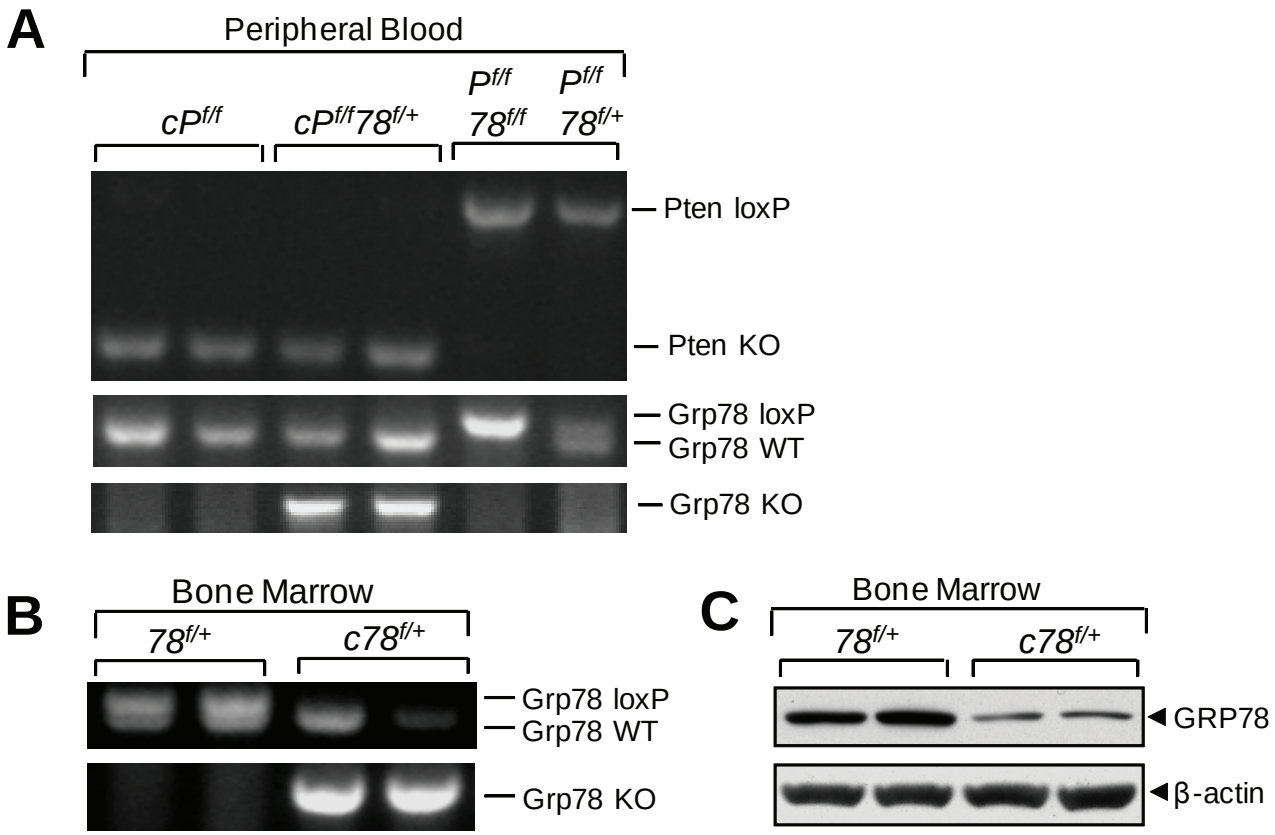

A
Peripheral Blood
cP f/f
cP f/f 78 f/+
P f/f 78 f/f
P f/f 78 f/+
Pten loxP
Pten KO
Grp78 loxP
Grp78 WT
Grp78 KO
B
Bone Marrow
78 f/+
c78 f/+
Grp78 loxP
Grp78 WT
Grp78 KO
C
Bone Marrow
78 f/+
c78 f/+
GRP78
β-actin

Figure S3

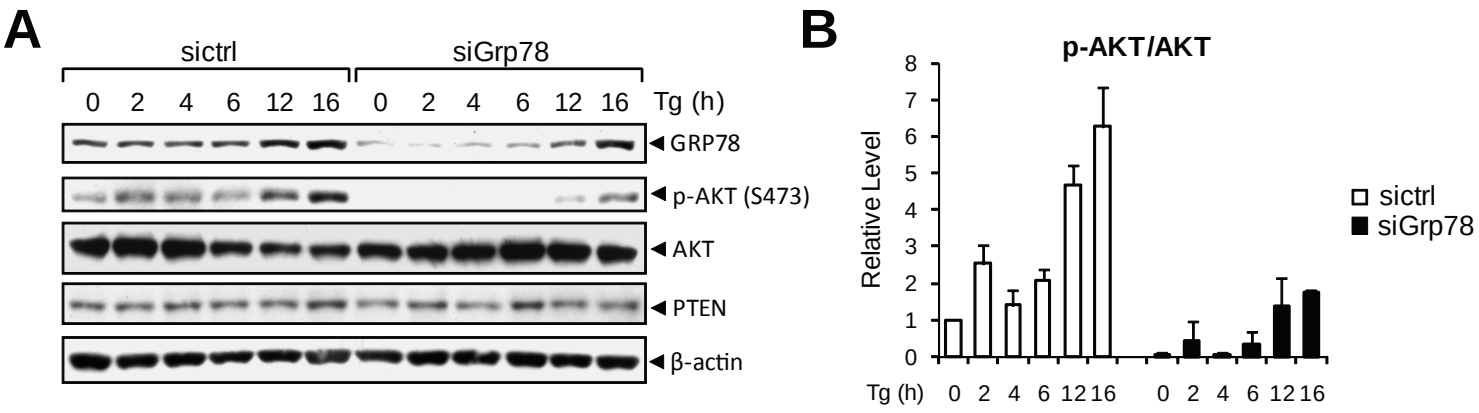

A
sictrl
siGrp78
0 2 4 6 12 16 0 2 4 6 12 16 Tg (h)
GRP78
p-AKT (S473)
AKT
PTEN
β-actin
B
p-AKT/AKT
Relative Level
0 1 2 3 4 5 6 7 8
Tg (h) 0 2 4 6 12 16 0 2 4 6 12 16
sictrl
siGrp78

Figure S4

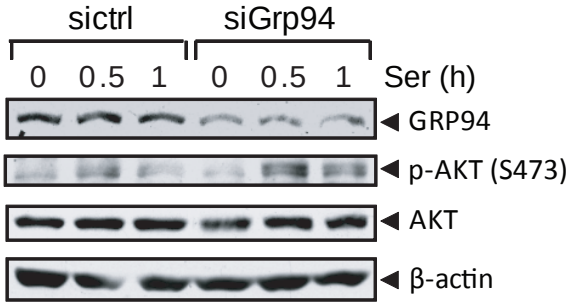
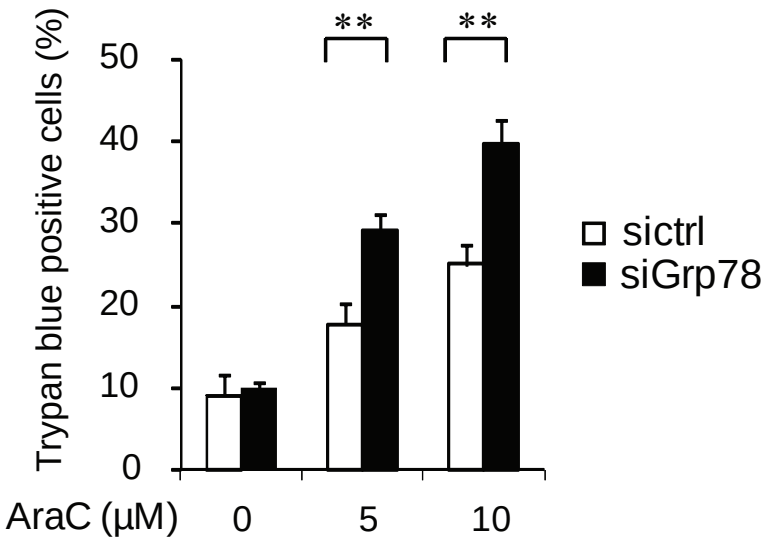


Figure S5


Trypan blue positive cells (%)
50
40
30
20
10
0
**
**
AraC (μM)
0
5
10
sictrl
siGrp78